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(54) Title: FORMULATIONS AND METHODS FOR ADMINISTRATION OF PHARMACOLOGICALLY OR BIOLOGICALLY ACTIVE COMPOUNDS

(57) Abstract: The present invention provides non-aqueous compositions which comprise a pharmacologically or biologically active compound, an emulsifier, a polyol, and benzyl alcohol. The compositions are useful for administering the pharmacologically or biologically active compounds which they contain to animals, plants, or ground surfaces. In preferred embodiments, the pharmacologically or biologically active compounds may be water-insoluble or water-labile. The compositions of the present invention allow these compounds to be solubilized and conveniently transported to a site of application in a non-aqueous form, and then diluted in an aqueous solution. In a particularly preferred embodiment, the compound is ivermectin and is administered in the drinking water of poultry. The compositions of the present invention may also contain multiple pharmacologically or biologically active compounds which are administrated simultaneously. The present invention also provides methods of administering the compounds. In the most preferred embodiment, the compounds may be administered in the drinking water of animals to be treated with the pharmacologically or biologically active compound. In other embodiments, the compositions may be topically applied to the animals or plants to be treated, or sprayed onto plants, animals, or a ground surface to be treated with the active compounds.

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FORMULATIONS AND METHODS FOR ADMINISTRATION OF PHARMACOLOGICALLY OR BIOLOGICALLY ACTIVE COMPOUNDS

FIELD OF THE INVENTION

The present invention is directed to formulations and methods for administering pharmacologically or biologically active compounds. In one embodiment, pharmacologically active compounds may be administered to vertebrates by diluting the formulation in the drinking water of the vertebrate. In a preferred embodiment the formulations may contain ivermectin or another parasiticide, and may be diluted in the drinking water of poultry for the treatment of a parasitic infection. The formulations and methods are useful for treating roundworms, cecal worms, lice, ticks, capillarial worms, and mite infections in poultry or other vertebrates.

In another embodiment, the pharmacologically active or biologically active compound may be a compound of agricultural interest which is administered to plants or soil surfaces by diluting the formulation in water and topically applying the diluted formulation to the plant or soil surface. In various embodiments the formulations may also be topically applied to animals.

BACKGROUND

Parasitic infections are common problems in a variety of vertebrates, including cattle, horses, swine, sheep, goats, and fowl. Various parasitic infections are also problematic in companion animals such as dogs and cats.

Chickens and other fowl are known to suffer from a variety of parasitic infections. Roundworms, cecal worms, capillarial worms, lice, ticks, and mites are among the common

parasites which may be associated with fowl and exact a substantial economic cost from the producers of fowl each year as well as raise health issues regarding the safety of the food supply.

Common methods of eliminating these parasites from fowl include the administration of piperazine to the drinking water or feed of animals. This method has had limited success due to the limited effectiveness of piperazine against these parasites. Treatment with tramisol has had somewhat better success but its use is limited by its very high cost. Therefore, animal caretakers are still in need of a cost-effective, efficacious method of eliminating these parasites.

Various useful pesticides exist which are either immiscible or unstable in aqueous solutions, making it impossible or impractible to dissolve these compounds in water for a spray-on application to crops or animals. Thus, the agriculture industry has been unable to utilize these pesticides with the ease of application and low cost which could be associated with the compounds if they could be simply dissolved in water and sprayed onto the plants, animals, ground surfaces to be treated, or applied directly to the insects to be treated.

SUMMARY OF THE INVENTION

The present invention provides non-aqueous compositions which comprise a pharmacologically or biologically active compound, an emulsifier, a polyol, and benzyl alcohol. The compositions are useful for administering the pharmacologically or biologically active compounds which they contain to animals, plants, or ground surfaces. In preferred embodiments, the pharmacologically or biologically active compounds may be water-insoluble or water-labile. The present invention provides methods and compositions in which these compounds can be solubilized and conveniently transported to a site of application in a non-aqueous form, and then diluted in an aqueous solution. In a particularly preferred embodiment,

the compound is ivermectin and is administered in the drinking water of poultry. The compositions of the pr[redacted] invention may also contain one or mor[redacted]rmacologically or biologically active compounds.

The present invention also provides methods of administering the compounds. In the most preferred embodiment, the compounds may be administered in the drinking water of animals to be treated with the pharmacologically or biologically active compound. In other embodiments, the compositions may be topically applied to the animals or plants to be treated, or sprayed onto plants, animals, or a ground surface to be treated with the active compounds.

DETAILED DESCRIPTION OF THE INVENTION

By "parasiticide" is meant any ectoparasiticide, acaricide, miticide, pediculicide, and antihelminthic.

By "anti-parasitic agent" is meant a miticide or an antihelminthic agent, including but not limited to ivermectin.

By "clinically effective amount" is that amount sufficient to have a therapeutically relevant effect on the treated organism. A therapeutically relevant effect relieves to some extent one or more symptoms in the treated vertebrate.

By "emulsifier" is meant a surface active agent promoting the formation and stabilization of an emulsion.

By "surfactant" is meant a surface active substance, or a substance which lowers the tension at the surface of contact between phases.

The present invention relates to formulations and methods for administering pharmacologically or biologically active compounds to vertebrates, plants, insects, and ground

surfaces. The compositions are provided in the form of a stabile, non-aqueous formulation. The composition may comprise a pharmacologically or biologically active compound, an emulsifier, a polyol, and benzyl alcohol. The compositions may be provided in a form suitable for dilution in aqueous solutions such as water, and the pharmacologically active compound may be a parasiticide.

The methods of the present invention involve providing the pharmacologically or biologically active compound in the form of a non-aqueous formulation of the present invention, diluting the formulation in an aqueous solution, and administering the formulation to the plant or vertebrate or ground surface to be treated. In a preferred embodiment, the formulation may be administered by diluting it into the drinking water of vertebrates to be treated with the pharmacologically active compound. In another embodiment, the formulation may also be administered parenterally. In yet a further embodiment, the formulation may be diluted in water or another aqueous solution and administered by spraying or otherwise topically applying to plants, agricultural crops, or a ground surface to be treated with a biologically active compound.

In a preferred embodiment, the formulation of the present invention may comprise a parasiticide or an anti-parasitic agent. In a particularly preferred embodiment, the formulation may contain ivermectin and may be administered by diluting it in the drinking water of poultry.

However, the person of ordinary skill in the art will realize that the formulations and methods of the present invention may be applied to a wide variety of compounds and administered in a variety of ways. The present invention may also be applied to a variety of compounds for topical administration to plants for the purpose of treating the plants with a pesticide or a nutrient. For example, the formulation may include a growth regulator or other nutrient and be diluted in an aqueous solution and sprayed directly onto plants or onto the soil

supporting the plants. In other embodiments, a compound of interest may be diluted into an aqueous solution and applied to a surface to be treated with the compound, such as a surface supporting plants, for the purpose of destroying foliage.

The present invention offers particular advantages in the administration of compounds which are water insoluble and/or water labile. It is found that water labile compounds are able to retain their stability in aqueous solutions for at least 10 days when administered in formulations of the present invention. It is also found that water insoluble compounds may be effectively diluted and administered in aqueous solutions, including drinking water, when administered as a formulation of the present invention. Water insoluble compounds are found to not form aggregates or clumps when formulated according to the present invention, and to disperse relatively uniformly in aqueous solutions to provide a steady dose of the pharmacologically or biologically active compound to the treated vertebrate drinking the water or a uniform dose to the plants, insects, or ground surface being treated with the formulation. The formulation may be diluted in any aqueous solution. In a preferred embodiment, the formulation is diluted and administered in the drinking water of a vertebrate.

Thus, the present invention makes available compositions and methods for conveniently and efficiently administering a wide range of pharmacologically or biologically active compounds to a wide range of vertebrates in a convenient manner. Many of these compounds could not formerly be easily administered in water due to the water-insoluble and/or water labile characteristics of the compound. For example, water insoluble and/or water labile compounds to which the present invention may be applied may include, but are not limited to: ivermectin, doramectin, avermectin, abamectin, milbemycin, amprolium, bacitracin, chlortetracycline, erythromycin, lincomycin/spectinomycin, neomycin, oxytetracycline, piperazine, sarafloxacin,

spectinomycin, sulfachloro-pyrazine, sulfadimethoxine, sulfamethazine, sulfaquinoxaline, tetracycline, tylosin, milbemycin, and spinosad. These compounds, which are often difficult to administer in drinking water or other aqueous solutions due to their lack of solubility or their instability in water, are provided as examples and are not intended to be limiting. The named compounds are meant to encompass their salt forms as well.

As noted above, ivermectin could not formerly be administered to birds or animals in drinking water because of the water-labile nature of ivermectin, which tends to quickly lose its pharmacological efficacy in aqueous solutions. Applying the principles of the present invention, we have achieved the complete elimination of roundworms and cecal worms from turkeys in three days by administering ivermectin in a formulation of present invention. The ivermectin formulation is conveniently administered by dilution of the formulation in the drinking water of the birds and requires no further effort since the compound's stability and potency in water is maintained for at least 10 days. The present invention may also be useful for treating a variety of other parasitic infections in poultry or other animals including, but not limited to, capillarial worms, mites, ticks, and lice.

Various pesticide compounds may be more conveniently and economically administered as a formulation of the present invention. For example, the phenyl pyrazole insecticides, pyrethroid insecticides and non-ester pyrethroid insecticides may all be administered according to the present invention. Thus, these compounds may be formulated according to the present invention and sprayed or otherwise applied to the plants, animals, or ground surfaces to be treated, or applied directly to the insects to be eliminated.

The person of ordinary skill in the art will identify other compounds, both existing and yet to be discovered, which may be utilized in the present invention and which are meant to be

encompassed within [redacted]cope of the present invention. Thus, the[redacted]cepts of the present invention are not limited to a particular group of compounds or for particular purposes. Rather, the present invention offers a formulations and methods for administering or delivering a compound of interest under a variety of circumstances.

The present formulations and methods are particularly advantageous in that a compound of interest may be formulated and transported as a non-aqueous formulation to a site of administration, and diluted in an aqueous solution at the site of administration to the animals, plants, insects, or surface to be treated. The formulations are especially advantageous when the compound of interest is water insoluble and/or water labile since the formulations of the present invention make it possible to administer these compounds in an aqueous solution in a convenient and cost-efficient manner.

The Formula

The formulations of the present invention are exemplified herein as the principles may be applied to ivermectin for administration to the drinking water of turkeys and other fowl. However, these examples are not intended to be limiting and the person of ordinary skill in the art will realize that these methods may be applied to administer a variety of pharmacologically and biologically active compounds such as those listed above and others to treat various illnesses and infections in a variety of animals, including but not limited to cattle, horses, swine, sheep, goats, and fowl.

The formulation of the present invention may comprise a clinically effective amount of a pharmacologically or biologically active compound, an emulsifier, a polyol, and benzyl alcohol. In a preferred embodiment, the formulation comprises (w/w):

2.02% ivermectin;

25.0% polysorbate 80 (e.g., Tween 80™, Uniqema, Wilmington, Delaware)

57.98% propylene glycol;

15% benzyl alcohol.

The formula of the present invention is prepared as follows: A kettle is charged with the benzyl alcohol and agitation is begun. The ivermectin or other compound of interest is added and the formula agitated until it dissolves. The vessel may be warmed to 40°C in order to speed dissolution. The propylene glycol and polysorbate 80 (Tween 80™ or its equivalent) are added The formula is blended for 15 minutes or until uniform. The sample may then be aliquoted, assayed, and packaged. This procedure results in a stable, non-aqueous formulation that is approximately 2.0% ivermectin.

The person of ordinary skill in the art will realize that substitutions may be made for one or more of the components of the formulation. For example, other polyols may be substituted for propylene glycol. Also, n-methyl-pyrrolidone (NMP) may be substituted for the polyol. Similarly, other surfactants may be substituted for the polysorbate 80 (Tween 80™), such as polysorbate 85, polysorbate 20, organosilicones, or polysiloxanes. These substitutions will preserve the chemical effect of the compound being substituted and are contemplated as being within the scope of the present invention. Without wanting to be bound by any particular theory, it is believed that the benzyl alcohol may be showing the surprising effect of solubilizing the polysorbate 80 in the propylene glycol. It is also believed that polysorbate 80 may serve as a

surface active agent which acts to partition the oil phase and water-soluble phases. It is believed that the polysorbate 80 may also facilitate the dissolution of the product in the water soluble phase upon dilution at the site of administration. It is also believed that the propylene glycol, or any polyol or n-methyl pyrrolidone, or any monohydric alcohol, may serve to solubilize the ivermectin and confer water solubility to the total formulation. Thus, the particular combination of components of the present invention combine to confer water solubility and water stability on water-insoluble and water-labile compounds such as ivermectin and other water insoluble or water-labile compounds.

Surfactants or surface active agents which are particularly suited for use in the compositions of the present invention are ionic or non-ionic surface active compounds generally well known in the art. Such agents generally have an oleophilic portion of the molecule, usually of hydrocarbon nature, and another polar portion of the molecule, which may be provided by various functional groups such as hydroxyl, sulfate, carboxyl, carbonyl, amino, nitro, amide, ether, sulfonate, phosphate, phosphite, etc. Examples of suitable classes of surface active agents which can be employed are alkali metal salts of fatty acids, alkali metal salts of sulfonated fatty acids, fatty acid glycerides, sulfonated or sulfated fatty acid esters or amides, alkali metal sulfates, alkali metal alkyl sulfonates, alkali metal aryl sulfonates, alkali metal alkyl lauryl sulfonates, quaternary ammonium halides, alkali metal salts of alkylated naphthalene, sulfonic acid, polyethylene sorbitol esters of fatty acids, fatty acid amides of alkanol amines, condensation products of ethylene oxide and polyalkylene glycols, sorbitan esters, alkyl substituted phosphoric acids, alkali metal salts of alkyl phenol sulfonates, polyalkyleneoxide polysiloxanes, etc.